REMARKS

Claims 1-32, 59-60 and 62 are the claims pending in the application. Applicants presently amend claims 1-16, 19 and 20, support for which can be found at least at pages 3-7 of the specification and the original claims as filed. No new matter is introduced. Entry of the amendment is kindly requested.

At paragraphs 1 through 6 of the outstanding Office Action, the Examiner indicates that claim 61 is cancelled; the amendment of claims 1-2, 59-60 and 62 is entered; and that claims 33-58 and 63-71 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

I. Withdrawn Objections and Rejections

At pages 2-4, paragraphs 6 through 15, the Examiner indicates that all objections and the 35 U.S.C. § 112, second paragraph; 35 U.S.C. § 112, first paragraph; 35 U.S.C. § 102(b); 35 U.S.C. § 102(a); and 35 U.S.C. § 103(a) rejections are withdrawn in light of Applicants' response filed November 14, 2006. Applicants thank the Examiner for withdrawal of all objections and the rejections in light of Applicant's Response filed November 14, 2006.

II. Claims 3-14, 17-32, 59-60, 62 Are Enabled Under 35 U.S.C. 112, First Paragraph

At page 4, paragraphs 16 through 17, the Office maintains the rejection of claims 3-14, 17-32, 59-60, 62, and newly rejects claims 15-16, under 35 U.S.C. 112, first paragraph as allegedly lacking enablement.

In making the first part of the rejection, the Examiner interprets the claim language "having amino acid sequences represented by," to include even only two amino acids of sequence 7, a variable region, and fragment of a single CDR. In making the second part of the rejection in the Office Action at page 6, the Examiner asserts that Applicants' invention is not sufficiently enabled for claims to antibody homologues and mutants even though the Examiner admits, "the art teaches methods of making antibody homologues and mutants by routine experimentation."

A. Claim Language

Solely to advance prosecution, Applicants herewith amend claims 1-16 without prejudice or disclaimer. The amendments overcome the first aspect of the rejection.

B. Enablement of Antibody Homologues and Mutants

Regarding the second aspect of the rejection, the genus of antibodies encompassed by the claims is well defined. The Examiner states that there are sufficient teachings of making antibody homologues and mutants by routine experimentation, thus the limitation in sequence length coupled with Applicants' teachings enable one of ordinary skill in the art to make the claimed homologues and mutants. The quantity of experimentation required to identify and mutate residues within Applicants' sequences is relative to the sequence length, and Applicants' sequences are recognized in the art as being significantly limited in number.

In the Office Action at page 7, the Examiner admits that "although the specification does provide information as to how to identify which sites to mutate, the specification does not demonstrate which residues can predictably be substituted and result in an antibody that has the claimed properties including increased affinity for the CD33." Applicants disagree. Holt *et al.* discloses domain antibodies comprising only three heavy chain CDRs. Holt *et al.* provides a detailed discussion of domain antibodies (dAbs), teaching that dAbs are antibody fragments consisting of only the variable region of the heavy chain (V_H) that retain the binding activity of the antibody from which they were derived. Holt *et al.* discloses human and murine versions of domain antibodies. As noted at page 486, column 2, third full paragraph, both human and mouse dAbs have been prepared that have high antigen specificity and binding affinity. As further noted in the conclusions section at page 489, the ability of dAbs to be affinity-matured by using *in vitro* selection, such as phage display, results in the rapid generation of specific, high-affinity dAbs.

One of ordinary skill in the art understands that changes to the heavy and light chain variable regions can easily be made without changing the specificity of the antibody. In this regard, Applicants refer the Examiner to the specification which references a large number of

published materials (e.g., journal articles and patents) that teach how changes can be made in an antibody sequence to make the homologues recited in the claims.

Applicants provide the Examiner with copies of Aires da Silva *et al.* (J. Mol. Biol., 340:525-542 (2004)), Tanaka *et al.* (J. Mol. Biol., 331:1109-1120 (2003), and Peterson (Advances in Monoclonal Antibody Technology: Genetic Engineering of Mice, Cells and Immunoglobulins, Peterson NC, ILAR J. 46(3):314-319 (2005)) to further educate the Examiner on these issues.

The specification specifically teaches how to conceive of, construct, test and use antibody homologues. Furthermore, Rajpal, *et al.* disclose that comprehensive optimization maps of an antibody site can be developed in facile and rapid manner. Rajpal, *et al.*, page 8466. In view of Applicants' teachings, and the disclosure of Rajpal, *et al.*, one of ordinary skill in the art would appreciate that changes to the heavy and light chain variable regions can easily be made without changing the specificity of Applicants' antibody.

Regarding the references upon which the Examiner relies, the disclosure of Paul is relied upon for demonstrating that an antibody's amino acid sequence and conformation are critical in maintaining antigen binding specificity and affinity. One of ordinary skill in the art would appreciate such a teaching but that, without further disclosure, the generic statement of Paul is insufficient to demonstrate that Applicants' invention is not enabled, since Applicants' antibody specifically binds to CD33 and, consistent with Paul, variants are based upon the same amino acid sequence and conformation. In addition, Paul appears to disclose that many aspects of an antibody molecule contribute to overall antigen binding specificity, including CDR length, sequence composition based on gene usage, localization in proximity to boundary regions, CDR backbone trajectory, CDR looping, the VH:VL dimer interface, as well as the "weak interactions" between the eiptope and paratope. In addition, Paul suggests that ultimately, "antigen-antibody interaction occurs only if the binding reaction releases enough free energy to be thermodynamically favored - affinity correlating exponentially with free energy." The cited reference shows that the Examiner's argument dramatically oversimplifies the state of the art and appears to misstate what Paul generally concludes - a plethora of molecular interactions, bonds

and conformations can influence antibody plasticity, not a single amino acid substitution or conformational change. Applicants' claims encompass the interactions discussed in the reference, since the "specifically binds to" limitation encompasses the parameters.

The Examiner relies on Rudikoff *et al.* and Coleman, broadly stating that the state of the art of antibody production is unpredictable, however this is inconsistent with the Examiner's earlier statement that "the art teaches methods of making antibody homologues and mutants by routine experimentation."

To support his arguments the Examiner relies on various antiquated references. The Examiner relies on Rudikof *et al.*, Paul, and Coleman to support his argument that the art is unpredictable. Rudikof *et al.* (1982), Paul (1993), and Coleman (1994) reflect the state of the art by as much as almost two decades prior to Applicants' filing date. Since 1982, the field of antibody technology has evolved to include advancements in antibody engineering. Advances in Monoclonal Antibody Technology: Genetic Engineering of Mice, Cells and Immunoglobulins, Peterson NC, ILAR J. 46(3):314-319 (2005). Peterson states that the smallest functional unit of an antibody is a CDR peptide . . . which varies from as few as eight to twenty amino acids (page 314-315 and Figure 1C), and that the affinity of a CDR is tested by its ability to compete with the parental antibody at its binding site. Peterson, page 315, line 5, left panel.

The Examiner improperly relies on Rudikoff *et al.* and Coleman broadly asserting that the state of the art of antibody production is unpredictable. Regarding Rudikoff *et al.*, the reference states that SI07 subclones are vastly antigen reactive, since only "0.1-1%" of the clones do not precipitate in soft agar assays. Page 1980, Results and Discussion, first sentence. Furthermore, at page 1982, the researchers state the opposite of what the Examiner concludes:

> "We have characterized another primary variant of S107 that has decreased antigen binding and a single amino acid substitution in the fifth residue of its J segment (39). However, it is clear that all substitutions need not and probably do not affect antigen binding. For example, the heavy chain from the P-Cho-binding myeloma protein M167 (35) differs from that of S107 at 13 positions (8 in hypervariable regions including a size difference) and yet has an association constant for hapten only slightly lower than S107. We have previously shown that, among anti-1,6-galactan-binding myeloma proteins, as many as eight or nine

substitutions may occur in hypervariable regions with no significant effect on hapten affinity or specificity (13)." (Emphasis added.)

It is clear that the result in the cited reference is an anomaly, and not representative of the state of the art.

In addition, Colman alone is insufficient to meet the requisite burden of proof required to establish a *prima facie* case of lack of enablement.[1] Colman also points out the opposite of that which the Examiner concludes, *i.e.*, that point changes in influenza virus neuraminidase yield predictable results, based on typical protein-protein interface behavior. Colman, page 34. With regard to somatic hypermutation, Colman states, "point mutations accumulating within the variable domains of antibody heavy and light chains are associated with increasing affinity of the antibody for antigen." Thus one of ordinary skill in the art would appreciate a significant degree of predictability in the art, based on the disclosures cited by the Examiner.

The Examiner also cites to Patti, as proof that the art is so unpredictable that one of skill would not know how to make and use polypeptides that are 90% identical to the recited sequences. The Examiner compares SEQ ID NO: 8 to a sequence disclosed by Patti, arguing that the art is so unpredictable that even though the VL sequence of the Patti antibody is 93% identical to SEQ ID NO: 8, the Patti antibody does not bind to CD33. The Examiner omitted amino acid 113 from SEQ ID NO: 8 in conducting the comparison.

Applicants compared Patti's light chain sequence with that SEQ ID NO.: 8 of the instant application and found it to be less than 93% homologous, as shown herewith:

[1] In Ex parte Harley, the Board of Patent Appeals and Interferences held that, in simply citing to Colman, "the examiner has not performed sufficient fact-finding under the appropriate legal standard in order to properly arrive at the conclusion that practicing the claimed invention would require undue experimentation. It may be that determining which of the myriad peptides encompassed by claim 1 on appeal possess the requisite binding property will involve further experimentation. But that does not mean that the claim is non-enabled. Absent further fact-finding and analysis by the examiner as to why the amount of experimentation needed in order to make the determination would be considered undue rather than routine, we do not find the examiner has established a prima facie case of non-enablement."

90.3% Identical

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                    1
60
35-006VLD-1     (1)
NIMXTQSPSSLAVSAGEKVTMSCKSSQSVLXSSNQKNYLAWYQQKPGQSPKLLIYWASTR
 muMy9-6 LC     (1)
NIMXTQSPSSLAVSAGEKVTMSCKSSQSVFXSSSQKNYLAWYQQIPGQSPKLLIYWASTR
                    61                                          113
35-006VLD-1     (61) ESGVPDRFTGSGSGTDFTLTISSVQXEDLAXYCCHQYLSSYTFGGGTELEIK-
 muMy9-6 LC    (61) ESGVPDRFTGSGSGTDFTLTISSVQXEDLAXYYCHQYLSSRTFGGGTKLEIKR
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Source: alignment software (vector NTI).

Furthermore, there is no support for the Examiner's conclusion that Patti's 12-9 antibody does not specifically bind to CD33. The 12-9 antibody of Patti is chimeric, whereas Applicants' antibody is not. Further, as discussed above in Paul, a single VL sequence does not necessarily prove that a specific affinity is conferred, since many interactions influence antigen specificity. Therefore, the reference does not provide support for the Examiner's assertion that the 12-9 antibody does not bind to CD33 nor is the homology calculation as high as the Examiner asserts.

III. Claims 1-8, 15 and 17-28 Are Novel Under 35 U.S.C. §102(b)

A. At page 9 of the Office Action, the Office rejects claims 1-8 and 15 under 35 U.S.C. 102(b) as being anticipated by Weitzhandler *et al.* Journal of Pharmaceutical Sciences, 83(12):1670-1675, December 1994.

Weitzhandler *et al.* do not specifically teach the antigen to which the My9-6 antibody binds and therefore, Weitzhandler *et al.* is not sufficiently enabling to qualify as prior art under §102(b). The My9-6 antibody was deposited in the ATCC on November 7, 2002, and therefore the antibody was not publicly available as of the 1994 publication date of Weitzhandler *et al.* Indeed, at page 9 of the Office Action, the Examiner admits that mere naming of the My9-6 antibody does not provide an enabling disclosure unless the My9-6 was made publicly available. Conclusive evidence that the My9-6 antibody was not publicly available is found in the 37 C.F.R. § 1.132 Declaration of Dr. Lambert, attached hereto. Dr. Lambert's Declaration states

that the antibody was not made available to the public but was used only by an ImmunoGen, Inc., employee within the corporation.

At page 9 of the Office Action, the Examiner states that the disclosure of My9-6 alone raises a presumption of operability, an argument in the alternative. The Examiner's assertion that the disclosure of My9-6 alone raises a presumption of operability, and is only overcome if Applicants provide evidence rebutting the presumption, is incorrect. A prior art reference "may yet be held not to legally anticipate the claimed subject matter if it is found not to be sufficiently enabling, in other words, if it does not place the subject matter of the claims within the possession of the public."[2] The Weitzhandler *et al.* reference fails to place the subject matter of Applicants' claims in the public, because one of ordinary skill in the art could not comprehend the invention, nor make it, upon review of the cited reference's disclosure of carbohydrates on IgG preparations. In fact, My9-6 is only disclosed by the reference as an immunoglobulin. Weitzhandler *et al.*, abstract. Since Weitzhandler *et al.* is not a patent, and therefore not entitled to a presumption of validity, thus no presumption must be overcome by the Applicants based on the disclosure of "My9-6" alone.

B. In the Office Action at page 9, the Office rejects claims 1-8, 15 and 17-28 under 35 U.S.C. 102(b) as being anticipated by CML NewsBytes, 10/24/2001, (www.cmlsupport.com/cmlnewsbytesarchives2.htm).

Applicants assert that the cited reference fails to enable Applicants' invention and therefore the reference cannot anticipate the claimed subject matter since one of ordinary skill in the art could not comprehend the invention, nor make it, upon review of CML NewsBytes. In addition, Applicants' arguments set forth above in IV A. are herein incorporated and applied to the cited reference.

[2] *In re Wilder*, 429 F.2d 447 (C.C.P.A. 1970).

C. At page 14 of the Office Action, the Office rejects claims 1-8, 15 and 17-28 under 35 U.S.C. 102(b) as being anticipated by BioCentury Part II. vol. 9. No. 48, pp. B1-B22, October 29, 2001.

The Examiner asserts that BioCentury Part II teaches murine monoclonal antibody My9-6 linked to the maytansinoid drug DM1. The Examiner alleges that the My9-6 referred to in the reference is "identical" to the claimed murine monoclonal antibody My9-6 comprising the heavy and light chain variable regions of SEQ ID NOs:7 and 8, respectively, and inclusive to the CDRs of SEQ ID NOs:1-6.

Applicants disagree. The cited reference is not enabled because the two sentence disclosure is insufficient to teach an antibody that specifically binds to CD33. The reference therefore cannot anticipate the claimed subject matter since one of ordinary skill in the art could not comprehend the invention, nor make it from the disclosure alone. The Examiner's assertion that the "My9-6 taught by BioCentury Part II necessarily comprises the heavy chain variable region of SEQ ID NO:7 and the light chain variable region of SEQ ID NO:8 and binds CD33" is entirely unsupported by the reference. In addition, Applicants' arguments set forth above in IV A are herein incorporated and applied to the cited reference.

Withdrawal of the 102(b) rejections is therefore kindly requested.

IV. Claims 3-14 Are Proper Under 37 C.F.R. §1.75(c)

At page 11 of the Office Action, the Office objects to claims 3-14 under 37 C.F.R. §1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim.

Solely to advance prosecution, Applicants herewith amend claims 3-4, 6-7, 9-10 and 12-13, placing the claims in independent form.

Applicants also amend dependent claims 5, 8, 11 and 14. Applicants' claim amendments overcome the Examiner's objection.

Withdrawal of the objection to claims 2-14 is therefore kindly requested.

V. Claims 1-32 Are Definite Under 35 U.S.C. §112, Second Paragraph

At page 12 of the Office Action, the Office rejects claims 1-32 under 35 U.S.C. §112, second paragraph, as being indefinite.

a. At page 12 of the Office Action, paragraph 22-23, the Examiner rejects claims 1-32 as indefinite for including "represented by..."

Solely to advance prosecution, Applicants herewith amend the claims.

b. At page 13 of the Office Action, the Examiner rejects claims 4, 7, 10 and 13 as indefinite for including "said amino acid."

Solely to advance prosecution, Applicants herewith amend the claims.

c. At page 14 of the Office Action, the Examiner rejects claims 19-20 as indefinite for reciting "derivatives thereof."

Applicants herewith voluntarily amend claims 19-20 solely to advance prosecution and without prejudice or disclaimer. The amended claims overcome the rejection.

Withdrawal of the rejection is therefore kindly requested.

VI. Claims 1-8, 15 and 17-32 Are Patentable Under 35 U.S.C. §103(a)

At page 15 of the Office Action, the Office rejects claims 1-8, 15 and 17-32 under 35 U.S.C. §103(a) as being unpatentable over Goldenberg *et al.* (U.S. Patent 6,759,045 B2, 8/8/2000, cited on F 892 mailed 6/14/06) in view of BioCentury Part II.

The Examiner admits that Goldenberg *et al.* do not specifically teach Applicants' antibody or conjugates thereof. The Examiner relies on the disclosure in BioCentury Part II for disclosure of the antitumor activity of My9-6 antibody, and the DM1 conjugate, for targeting myeloid leukemia cells.

However, the two sentence disclosure of BioCentury Part II fails to teach an antibody that specifically binds to CD33 and therefore cannot read on the claimed subject matter since one of ordinary skill in the art could not comprehend the invention, nor make it from the disclosure alone. The Examiner's assertion that the "My9-6 taught by BioCentury Part II necessarily comprises the heavy chain variable region of SEQ ID NO:7 and the light chain variable region of

SEQ ID NO:8 and binds CD33" is entirely unsupported by the BioCentury Part II disclosure. Since the reference does not disclose an essential feature of the invention, a *prima facie* case of obviousness cannot be set forth.

It is impossible for one of ordinary skill in the art to be motivated or to have a reasonable expectation of success to conjugate Applicants' claimed antibody since the antibody is not taught in BioCentury Part II. In addition, by the Examiner's own admission, Goldenberg *et al.* fail to compensate for the lack of teaching and guidance in BioCentury Part II.

Withdrawal of the obviousness rejection is therefore kindly requested.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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